Tryptamine-Derived Isocyanides I Have Known and Loved

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Summary

Tryptamine-Derived Isocyanides I Have Known and Loved:

From Multicomponent Reactions to Natural Product Synthesis

Driven by natural selection, Nature has composed a preferred collection of molecular fragments that have shaped its rich repertoire of chemical structures. Tryptamine can be considered as such a so-called privileged structure, as it is incorporated in a great variety of natural occurring alkaloids. Especially monoterpenoid indole alkaloids are highly abundant and have attracted great interest from the organic chemistry community. Woodward's total synthesis of strychnine was an important landmark, demonstrating the possibility to synthesize natural products of such complexity. Although nowadays many monoterpenoid indole alkaloids have been synthesized, alternative synthetic strategies continuously appear in the literature, mainly with the aim to showcase new synthetic methodologies. **Chapter 1** presents an overview of the total syntheses of *Aspidosperma* and *Strychnos* type alkaloids via dearomatization strategies of indoles. The work described in this thesis was based on our interest to exploit the reactivity of tryptamine-derived isocyanides in alternative synthetic approaches towards these classes of monoterpenoid indole alkaloids (Figure 1).

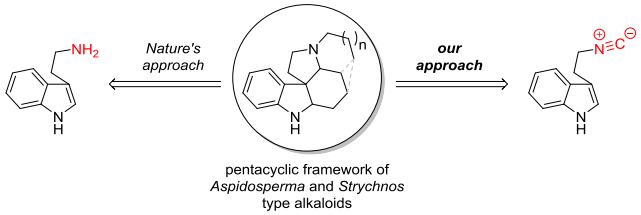
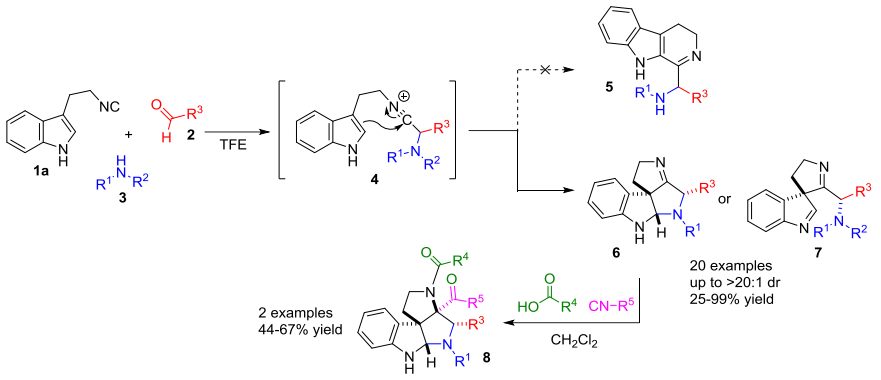


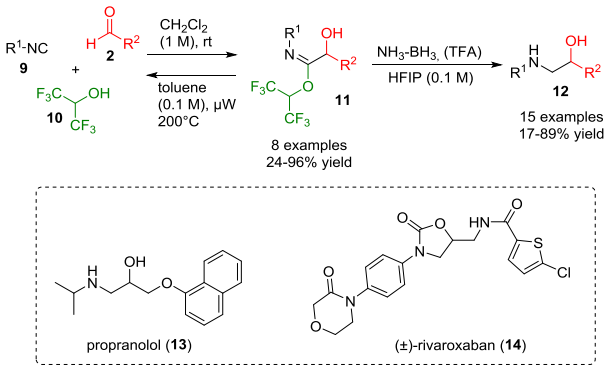
Figure 1. Tryptamine-derived isocyanides in the synthesis of the pentacyclic framework of *Aspidosperma* and *Strychnos* type alkaloids.

To become familiar with the chemistry of tryptamine-derived isocyanides, we initially explored their reactivity in Ugi-type chemistry (**Chapter 2**). The concept utilizes the nucleophilicity of the indole C3 position to intercept the intermediate nitrilium ion, which is generated after attack of the isocyanide on the imine (Scheme 1). Ji *et al.* had already shown the viability of this concept with tryptamine-derived isocyanides (**1**) in conjugate additions with electron-poor Michael acceptors. To by-pass the classical Ugi-4CR, we excluded the carboxylic acid and screened several Lewis and Brønsted acids for imine activation. Fortunately, when switching to TFE or HFIP as the solvent the mildly acidic solvents sufficed to facilitate the desired transformations. This interrupted Ugi reaction tolerates a wide range of substituents on all reactants and could be connected to a second Ugi reaction in a one-pot process to afford highly decorated spiroindolines **8**. Unfortunately, our efforts to develop a catalytic enantioselective variant of this reaction were not succesful (max. *ee* = 17%). However, with the recent discovery of a catalytic asymmetric procedure for classical Ugi reactions by Tan *et al.*, we expect that a suitable chiral phosphoric acid can generate similar enantioselectivities in this interrupted Ugi reaction (**Chapter 6**).



Scheme 1. Interrupted Ugi reactions with tryptamine-derived isocyanides.

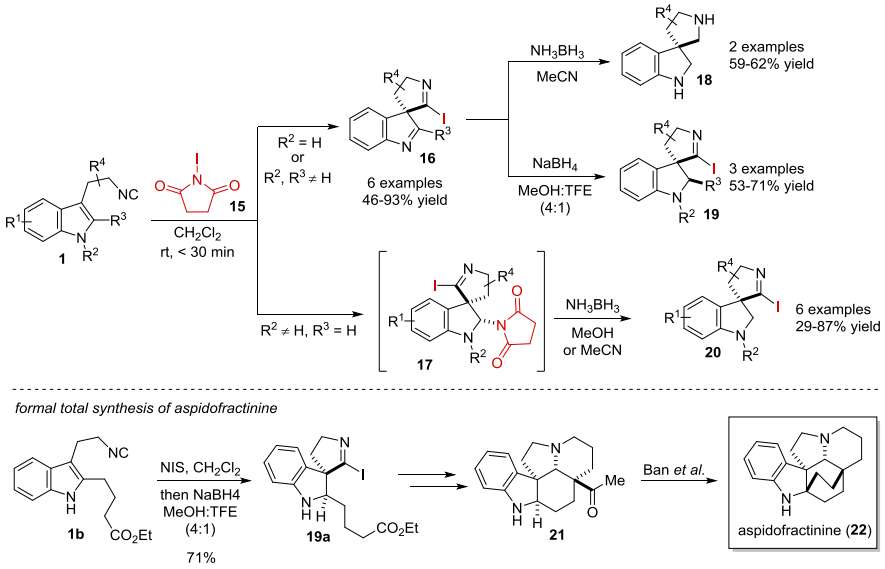
Intrigued by the efficient spirocyclization of tryptamine-derived isocyanides in interrupted Ugi- and Passerini-type reactions, we studied the isocyanide scope by employing other tethered electron-rich arenes under similar conditions. Surprisingly, only the formation of imidate **11** was observed without a trace of the envisioned Bischler-Napieralski-type product (**Chapter 3**). Motivated by this unexpected Passerini-type reaction with HFIP as the acid component, we investigated the generality of this reaction. Switching to stoichiometric amounts of HFIP in CH_2Cl_2 (1 M) as the solvent resulted in rapid conversion (1-4 h) and compatibility with a broad range of isocyanides and aliphatic aldehydes. The synthetic utility of this method was greatly enhanced when we combined it with an *in situ* reduction to directly give β-amino alcohols **12**. This one-pot, two-stage protocol was applied to the synthesis of propranolol (**13**) and (±)-rivaroxaban (**14**). Finally, the Passerini-type imidates were shown to undergo an unprecedented retro-Passerini-type reaction under microwave irradiation.



Scheme 2. HFIP as an acid component in Passerini-type reactions.

Continuing the work on tryptamine-derived isocyanides we extended the reactivity towards electrophilic halogenating reagents as described in **Chapter 4**. Initial experiments showed

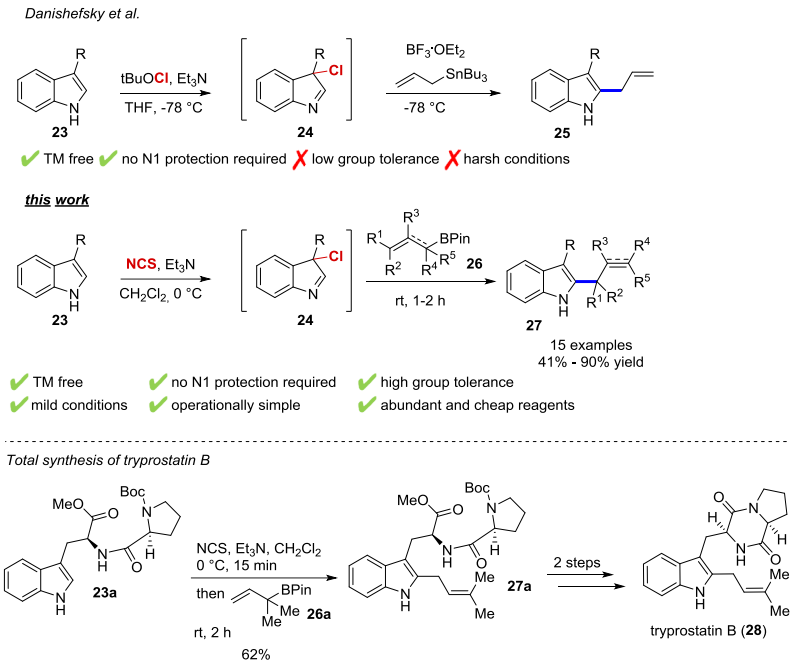
that isocyanides **1** react very efficiently with NIS in iodospirocyclization reactions to form surprisingly stable spirocyclic products **16**. After this discovery, we explored the reactivity of these products in several post-modifications. Intriguingly, nucleophilic additions were typically chemoselective towards the imines rather than the imidoyl iodide moiety. With respect to the isocyanide scope, we found that a wide range of substituents was tolerated on the tryptamine backbone (Scheme 3). In general, product stability increases after reduction of the initially formed imines (or aminals in case of **17**) to form spiroindolines **19** or **20**. Based on these insights, we devised a synthetic route to 19-oxoaspidospermidine (**21**) starting from isocyanide **1b**, thus establishing a formal total synthesis of aspidofractinine (**22**). We believe that this strategy has great potential in the synthesis of a wider range of *Aspidosperma* and *Strychnos* type alkaloids. Some suggestions, together with preliminary results in asymmetric spirocyclizations, are discussed in **Chapter 6**.



Scheme 3. NIS mediated iodospirocyclization reactions with tryptamine-derived isocyanides.

In search of procedures that can be utilized to conveniently synthesize C2-substituted tryptamine-derived isocyanides, we noticed that short and operationally simple procedures were very limited. Particularly C2 allylation procedures lacked the practical simplicity that we desired, as most approaches require the installation of a directing group at the N1 position. In our quest to tackle this problem, we captured the concept of nucleophilic additions on *in situ*-generated 3-chloroindolines **24** reported earlier by Danishefsky *et al.*, and tweaked it into a milder and more general C2 allylation procedure by simply including allylboronates **26** and by slightly changing the chlorinating conditions (**Chapter 5**). The procedure tolerated a range of C3-subsituted indoles and allylboronates, and the potential

of our method was highlighted in the synthesis of tryprostatin B (**28**). Finally, we believe that the mild reaction conditions and high functional group tolerance are promising features which can be exploited in peptide stapling (**Chapter 6**).



Scheme 4. C2 allylation procedure via allylborations of *in-situ* generated 3-chloroindolenines.

The research described in this thesis originates from our idea to utilize tryptamine-derived isocyanides in natural product synthesis. Driven by curiosity, we successfully realized the formal total synthesis of aspidofractinine. Apart from this synthesis, we believe that more natural product syntheses will arise that exploit the reactivity of tryptamine-derived isocyanides. To obtain optically pure spiroindoline products, preliminary studies based on some initial concepts gave overall unsatisfactory *ee*'s. Future efforts should be directed to further explore these initial concepts and perhaps develop alternative strategies. Furthermore, our studies revealed several new insights in both indole and isocyanide chemistry. Considering this, we hope that curiosity-driven research remains actively promoted as it often leads to unexpected, yet fruitful discoveries.